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(54) Title: GRANULES FREE OF EXCIPIENTS

(57) Abstract

Granules free of excipients suitable for all pharmaceutical formulations have been provided for. Also a process to prepare said granules by employing a sieving device preferably comprising an air jet system has been provided for.

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GRANULES FREE OF EXCIPIENTS

The present invention relates to granules free of excipients and a process to prepare the same.

Technical background and field of invention

It is generally known that crystalline antibiotic powder itself is not suitable for the manufacturing of tablets and capsules containing oral grade antibiotics such as penicillins or cephalosporins because the crystalline material has no satisfactory flowability and density so that controlled dosage per tablet or capsule is not guaranteed. Therefore, normally a granulate is produced first by mixing the crystalline product (1-30 μm) with a small amount of organic solvent (e.g. alcohol and/or water). It is preferred then to admix other components as binders (e.g. PVP) and fillers (e.g. lactose) for obtainment of granulates with satisfactory particle size distribution and strength. However, it will not be possible to achieve a high dosage per tablet unless relatively large tablets are made.

The granulation process generally takes place in a high shear mixer granulator by which dense particles of a suitable particle size distribution are produced. After the granulation process the material (particles of approximately 400-500 μm average diameter) is dried. It is found that while using only water as binding agent (i.e. no alcohol, no further binding agents) the batch-wise operated high shear granulators can not give a satisfactory particle size distribution while excessive fouling of the apparatus occurs.

Difficulties one may encounter by using wet granulation are:

- decomposition of ß-lactam antibiotics because of use of water and/or organic solvents combined with elevated temperature during granulation,
- the use of organic solvents is restricted by governmental rules concerning environmental protection,

- the process is labour intensive, expensive and time consuming because of the large number of processing steps like mixing, granulating, wet sieving, drying etc.,
- a lot of energy is needed to dry the wet granules,
- granules produced by wet granulation are rather porous, high bulk volumes are not or difficult to reach with the consequence that high dosages in gelatin capsules are often not possible,
- binder dissolved in a binder solution or dry mixed with the compound to be granulated can give problems with a homogeneous distribution because of their sticking nature with as result an inhomogeneous composition which can cause differences in dissolution and/or tablet hardness between dosage forms of one batch and therefore differences in bioavailabity,
- variable "residual free water content" is added to the quality control analysis.

Difficulties one may encounter by using dry granulation are:

- a lot of dust is produced during the slugging or roller compaction process and in some cases, for example such as amoxicillin, this dust sticks to the coarser particles and can not be separated by currently applied vibrating sieves,
- dust may deteriorate the flow properties of granules, which inadequate flow properties result in a larger weight variation of the dosage forms,
- dust is also responsible for air born ß-lactam antibiotics particles which can cause allergic reaction,
- over compaction of initial granules gives a lower dissolution rate,
- possible over lubrication coupled with hydrophobisation due to use of a too high amount of hydrophobic lubricant and hydrophobisation decreases the dissolution rate.

In German patent application DE 2251250, a process for relatively small tablets containing a high amount of antibiotic using a granulate prepared with a small (5-15%) amount of excipients (e.g. crystalline cellulose, binder, talc) has been described. European patent EP 281200 describes a pharmaceutical granulate comprising 35-45 wt% microcrystalline cellulose

prepared by wet granulation, which granulate disintegrates quickly when immersed in water. Also, in PCT applications WO 9116893 and WO 9219227, for example, the antibiotic has been described to be mixed with excipients (e.g. an effervescent couple of excipients or intra-granular disintegrant, flavour, magnesium stearate) for granulation using slugging or a roller compactor for compacting. Thereafter, the granules have been sieved to the desired particle size and finer material is recycled to the compaction process. In PCT application WO 9528927, a pharmaceutical tablet formulation having a structure comprising compacted granules of amoxicillin and clavulanate in a weight ratio of 6:1 to 8:1, excipients and a coating of polymers has been described.

Surprisingly it is found that granules without any excipients can be prepared. These have nowhere been described or suggested in the prior art.

Summary of the invention

The present invention provides granules being free of excipients, for instance antibiotic and antihypercholesterolemic ones and preferably also substantially free of solvents. These granules are of a particle size between about 50 μm and 1500 μm, preferably between about 125 μm and 1000 μm.

Examples of antibiotic granules are those of penicillins, cephalosporins, tetracyclines and macrolides. Examples of penicillins are preferably amoxicillin, ampicillin, penicillin V, oxacillin, cloxacillin, flucloxacillin, dicloxacillin and pharmaceutically acceptable salts thereof, preferably potassium salt of penicillin V, sodium salt of cloxacillin, sodium salt of flucloxacillin and sodium salt of dicloxacillin. Examples of cephalosporins are preferably cephalexin, cefaclor, cefadroxil and cephradine. Examples of tetracyclines are tetracycline, chlorotetracycline, oxytetracycline, doxycycline, minocycline, demeclocycline and acid salts thereof, preferably the HCl salts. Examples of macrolides are preferably erythromycin, clarithromycin, roxithromycin, azithromycin and stearates, estolates, propionates, ethylsuccinates thereof.

Examples of antihypercholesterolemic compounds are lovastatin, simvastatin and pravastatin.

Furthermore, a process to prepare said granulates has been provided for. The process comprises of feeding, for example, an antibiotic powder corresponding to said granules to a roller compactor to produce compacts, followed by milling to give granules. These granules are, then, sieved with a sieving device to separate the granules from fine particles with a size of <150 μm, preferably <125 μm. The sieving device preferably comprises an air jet system. The fine particles are optionally recirculated to the roller compactor.

The granules, prepared according to the present invention, are suitable to prepare oral dosage forms such as tablets, capsules, syrups, sachets, dry instant or ready to use and multiple or single dose. According to the another embodiment of the invention, the oral dosage form, comprising granules free of excipients also contain a β-lactamase inhibitor such as potassium clavulanate, preferably in granule form. Said granules can also be used in Dose Sipping devices.

Detailed description of the invention

The granulation method, wherein the use of excipients has been avoided, consists of dry granulation by using compaction forces to build up agglomerates. This may be performed by slugging or roller compacting. The compacts are milled and, then, sieved with a sieving device. The separation of fine particles from coarse granules may be carried out by a dry sieving or wet sieving procedure.

During dry sieving, the milled compacts are placed on the sieve and air is blown through the bed of milled compacts to separate the granules from the fine particles. The sieving device comprises preferably an air jet system. Furthermore, the sieving device can be coupled directly to the roller compactor or stand separately from the same.

The application of this granulation method results in granules of penicillins, cephalosporins, tetracyclines, macrolides and antihypercholesterol compounds with a satisfactory particle size distribution, viz. between 50 μm and 1500 μm, preferably between 125 μ and 1000 μm. Moreover, these granules are preferably substantially free of organic solvents and/or water, because during the process of compaction, use of these solvents are usually avoided. The only traces of solvent(s) that may be present in the said granules are either already present in the starting compound or result from wet sieving operation.

For example, a certain amount of antibiotic powder to be granulated, for instance amoxicillin trihydrate, is fed to a roller compactor. The compact materials are milled and, thereafter, sieved by using an air jet system. The sieving device is coupled directly to the roller compactor in order to avoid extra steps or stands separately. The fine particles, preferably the material < 125 μm, are recycled to the roller compacting process.

The granules free of excipients can be used for all formulations to produce chew, swallow, disperse, effervescent or normal tablets of all sizes, forms and weights, also to fill hard gelatin capsules and to formulate dry syrups and for administering drugs with the help of a dose sipping device. These granules can also be used, for instance, in a pharmaceutical composition as a tablet of amoxicillin trihydrate produced from granules of amoxicillin trihydrate and potassium clavulanate (in ratio of 1-20:1 as, for example, described in European patent EP 49061 and International patent application WO 9709042) as a powder or in granule form.

To produce tablets, only excipients have to mixed with the granules and tablets can be pressed. To fill hard gelatin capsules no excipients are necessary, the granules can directly be filled into capsules or when fast running capsules filling machines are used, some lubricant like magnesium stearate can be mixed with the granules to facilitate the filling process.

To formulate dry oral syrups, flavours, bulking agents such as sugars and preservatives are often used. These excipients are mixed with the

granules and bottles are filled thereof. Optionally a premix of excipients is prepared and filled into bottles after which the granules are added separately.

For Dose Sipping Devices, for example, the granules can be placed over a support in a tube having a liquid inlet end and a liquid outlet end; excipients can also be placed over the support, together with the drug granules. Oral administration of therapeutical agents with the help of a Dose Sipping Device has been described in European patent application EP 383503.

The preparation of granules without the use of excipients, according to the present invention, has the following advantages over the existing methods:

- economy in labour, time, equipment, energy and space,
- it eliminates problems in granulation processes due to heat and moisture,
- it allows for disintegration of dosage forms into primary drug particles followed by a high dissolution rate because no binders have been used,
- the resulting granulates show excellent flow properties and almost no dust at all,
- the resulting granulates containing antibiotics or antihypercholesterol compounds show all-around technological properties for the production of all oral dosage forms like tablets, capsules, syrups, sachets, dry instant or ready to use, multi dose or single dose and for dose sipping devices,
- as not any excipient is used for the production, these all-round granulates provide a large flexibility.

Also the preparation of a pharmaceutical composition of granules of β-lactams, for instance amoxicillin trihydrate and a β-lactam inhibitor, for instance clavulanic acid or a pharmaceutical acceptable salt thereof, or sulbactam, preferably in the granule form, have been provided for. The granules of the β-lactam inhibitor optionally contain an excipient.

The invention will now be described with reference to the following examples, which are not to be constructed as being limited to the invention, and are provided purely for illustrative purposes.

Preparation 1

Production of amoxicillin granulate by roller compacting using conventional vibrating sieving.

Amoxicillin trihydrate powder was fed to a Fitzpatrick roller compacter type Chilsonator 4L X 10D. The used rolls had a diameter of 25.4 cm and a roll wide of 10.2 cm, the roll surface was sinus waved grooved, the roll gap was 3.1 mm. The roll speed was 11 rpm, the horizontal feeder speed was 17 rpm, the vertical feeder speed 450 rpm and the applied roll pressure 1100 psi.

The compacts were milled using a Fitzmill type DAS 06 equipped with type 425 blades adjusted with the sharp ends forward, the mill speed was 1500 rpm and the used screen had apertures of 2 mm. The milled material was sieved using a Midwestern vibrating sieve with apertures of 150 μm.

The material >150 μm, collected from the 150 μm sieve was the final product. The fines <150 μm were recycled from the receiver to the roller compacting process.

Example 1

Production of amoxicillin granulate by roller compacting using air sieving.

The same roller compacting procedure as mentioned under example 1 was performed except for sieving the milled material.

Instead of a vibrating sieve, a Minox sieve type MTS 1200 equipped with an air jet system was used. The sieve applied had a diameter of 120 cm and apertures of 150 μm. The air was escaping upwards from a rotating perforated blade fixed horizontal under the sieve. By this action the fine particles were blown of from the coarse particles and sucked downwards through the sieve to the receiver by the action of an under pressure.

The fines < 150 μm were recycled from the receiver to the roller compacting process. The material > 150 μm, collected from the 150 μm sieve, was the final product.

Example 2

Separation of fines from coarse amoxicillin granulate particles of preparation 1 for analytical purpose.

The following three analytical sieving methods were used to separate fine from coarse particles amoxicillin granulate:

Vibrating sieve:

Sieves with a diameter of 20 cm, apertures of 125, 250 and 1000 μm and known weight were stacked with the 1000 μm sieve on top and a collecting pan with known weight on the bottom. 80 g of amoxicillin granulate was weighed and added to the top sieve. The sieving machine, a Retch type Vibro, was turned on for 10 minutes using a vibration power setting of 80. The amounts of amoxicillin were determined by weighing the sieves and collecting pan.

Wet sieve:

Sieves with a diameter of 75 mm, apertures of 125, 250 and 1000 μm and known weight were stacked with the 1000 μm sieve on top and a collecting pan on the bottom. 3 g of amoxicillin granulate was weighed and added to the top sieve with the aid of n-hexane which is a non-solvent for amoxicillin. Applying small amounts of a total of 200 ml n-hexane the top sieve was flushed. The n-hexane suspension in the collecting pan was filtered with the aid of a filter paper of known weight. The sieves and filter were dried in a ventilation cabinet. The amounts of amoxicillin were determined by weighing the sieves and filter.

Air sieve:

A sieve with a diameter of 20 cm, known weight and apertures of 125 μm was put on a Hosokawa Alpine air sieve type 200 LS-N, 20 g amoxicillin

granulate was weighed and put on the sieve. The air sieve was activated during 3 minutes, whereafter the amount of amoxicillin was determined by weighing the sieve.

The test was repeated with a 250 and 1000 μm sieve.

Table 1 Results of three sieve test methods applied on amoxicillin granulate of preparation 1

sieve method	> 1000μm	< 1000μm and > 250μm	< 250μm and > 125μm	< 125μm
vibrating sieve	11.0%	78.7%	78.7%	0.7%
wet sieve	9.4%	58.4%	6.2%	25.9%
air sieve	9.1%	58.3%	5.8%	26.0%

Using the vibrating sieve method it is not possible to separate the fine from the coarse particles. The air sieving method, which gives comparable results with the wet sieving one, is very reliable.

These results show clearly that amoxicillin granulates produced with the conventional roller compacting process contain a lot of fine particles, which can not be separated from the coarse particles by a conventional vibrating sieving method.

Example 3

Flowability of amoxicillin granulate of preparation 1.

The following two analytical methods were used to determine the flowability of the amoxicillin granulate:

1. Flowability funnels after Lerk (from Pharmaceutical Technology, Post-Academic Course in 1977):

Five Funnels, with varying diameter of 2.5 - 5 - 8 - 12 and 18 mm, were positioned vertical with the small opening downwards. The funnel with the smallest opening was filled with amoxicillin granulate while the opening

was closed with a finger. The flowability of the granulate was observed when the finger was removed. If the granulate did not flow through the funnel the test was repeated with a funnel with a one step larger opening. The flowability of the granulate was determined by a smooth flow through the funnel with the size of the smallest opening.

The class of flowability was determined using the classification of table 2.

Table 2 Flowability classification using different funnel openings according to Lerk

class	diameter funnel	flowability
1	2.5 mm	excellent
2	5 mm	good
3	8 mm	amply sufficient
4	12 mm	just sufficient
5	18 mm	poor

The amoxicillin granulate of example 1 did not flow through the funnel with a diameter of 18 mm so this material shows a poor flowability.

2. Compressibility or Hausner ratio (see The Theory and Practice of Industrial Pharmacy, 3rd edition, 1986 page 184 and Powder Testing Guide, 1987 page 91 - 93):

A graduated cylinder of 250 ml was filled carefully with amoxicillin granulate up to the 250 ml mark, the weight of the amoxicillin was determined and the loose bulk density was calculated in g/ml.

The cylinder was tapped using an Engelsmann Volumeter until the volume did not change more than 2 ml after 100 taps, the decreased volume was determined and the tapped bulk density was calculated in g/ml.

The compressibility was calculated according to the following formula:

$$\frac{\text{(tapped bulk density - loose bulk density) x 100\%}}{\text{tapped bulk density}}$$

The Hausner ratio was calculated according to the following formula:

$$\frac{\text{tapped bulk density}}{\text{loose bulked density}}$$

The class of flowability was determined using the classification of table 3.

Table 3 Flowability classification using loose and tapped bulk density

compressibility	Hausner ratio	flowability
5 - 15%	1.05 - 1.18	excellent
12 - 16%	1.14 - 1.19	good
18 - 21%	1.22 - 1.27	fair - passable
23 - 35%	1.30 - 1.54	poor
33 - 38%	1.49 - 1.61	very poor
> 40%	> 1.67	very, very poor

The amoxicillin granulate of example 1 showed the following results:

- loose bulk density : 0.59 g/ml
- tapped bulk density : 0.84 g/ml
- compressibility : 30%
- Hausner ratio : 1.42.

These results indicate a poor flowability.

Example 4

Separation of fine from coarse amoxicillin granulate particles of example 1.

The air sieve method mentioned in example 2 was applied on amoxicillin particles.

The results are presented in table 4.

Table 4 Results air sieve test applied on amoxicillin granulate of example 2

sieve method	> 1000μm	< 1000μm and > 250μm	< 250μm and > 125μm	< 125μm
air sieve	0.1%	81.4%	14.7%	3.8%

Example 5

Flowability of amoxicillin granulate of example 1.

The flowability method using the funnels according to Lerk mentioned in example 3 was used. The amoxicillin granulate of example 1 did flow smoothly through the funnel with a diameter of 5 mm so this material showed a good flowability. The flowability method according to the compressibility / Hausner ratio measurement was used.

The amoxicillin granulate of example 1 showed the following results:

- loose bulk density: 0.52 g/ml
- tapped bulk density: 0.60 g/ml
- compressibility: 13%
- Hausner ratio: 1.15

These results also indicate a good flowability.

Example 6

Production of tablets containing amoxicillin granulate of example 1

2.15 kg of amoxicillin granulate (prepared from amoxicillin trihydrate according to example 1), 0.49 kg of microcrystalline cellulose (Avicel®) PH112 with a water activity of less than 0.2 at 25 °C) and 0.1 kg of hydrogenated vegetable oils (Lubritab®) were weighed and mixed in a Turbula mixer and

subsequently about 5000 tablets were produced on Korsch KO1 excenter tablet press equipped with flat 12 mm punches. The characteristics of the tablets were:

diameter 12 mm; thickness 4.3 mm; weight variation according to U.S. Pharmacopoeia XXIII 1994, The United States Pharmacopoeial Convention Inc. Rockville, MD, USA; hardness between 100 and 130 N, disintegration 30 seconds in water of 20 °C.; dissolution more than 85% of the labelled amount of amoxicillin dissolves within 30 minutes by using the method as described in U.S. Pharmacopoeia XXIII 1994, The United States Pharmacopoeial Convention Inc. Rochville MD, USA.

Example 7

Production of four different formulations of tablets containing amoxicillin granulate of example 1

Compositions of the tablet formulations

Materials	Formulations (mg per tablet)			
	A	B	C	D
Amoxicillin granules from example 2	287.5	287.5	287.5	287.5
Lactose anhydrous (Pharmatose DCL 21)	725.0			
Lactose monohydrate (Pharmatose DCL 15)		725.0		
Dibasic Calcium Phosphate dihydrate (Emcompress)			725.0	
Microcrystalline cellulose (Avicel PH 112)				975.0
Maize starch B	250.0	250.0	250.0	
Magnesium stearate	20.0	20.0	20.0	20.0

Preparation of the tablets

Amoxicillin granules and the excipients (except magnesium stearate) were weighed according to the above compositions and mixed during 5 minutes in a Turbula mixer, the total weight of the materials was about

100 g. Magnesium stearate, which was previously sieved through 90 μm, was added and mixed during 1 minute.

Finally, tablets were pressed using a Korsch EKO excenter tablet press equipped with flat punches with a diameter of 12 mm.

Analytical results of tablet tests (between brackets the standard deviation)

Formulation	Weight [mg] (N = 20)	Thickness [mm] (N = 10)	Hardness [N] (N = 10)	Friability after 100 revolutions [w/w%] (20 tablets)	Disintegration in tap water without stirring [sec] (N = 3)	Dissolution after 30 min. in 900 ml water of 37°C using paddles at 75 rpm (N = 4)
A	411.4 ± 12.9	3.149 ± 0.019	104.9 ± 26.3	0.46%	130	100% *
B	397.6 ± 3.9	3.149 ± 0.019	123.7 ± 21.3	0.38%	70	100% *
C	400.8 ± 4.4	2.842 ± 0.018	114.4 ± 15.9	0.44%	57	100% *
D	392.1 ± 5.9	3.106 ± 0.016	120.8 ± 15.7	0.17%	50	100% *

* % released of total amount of amoxicillin in tablet

Example 8

Preparation of capsules containing amoxicillin granules

Amoxicillin granulate (prepared from amoxicillin trihydrate according to example 1) was filled into hard gelatine capsules on a Robert Bosch GKF 1200 S capsule filling machine using continuous motion with tamping and a speed of about 65,000 capsules per hour.

Example 9

Preparation of tablets containing amoxicillin granules and potassium clavulanate granules

During the preparation procedures, the temperature was between 20 and 25 °C and the relative humidity < 20%.

Amoxicillin granules were prepared according to example 1, the water activity of the granules was less than 0.2 at 25 °C, which was obtained by drying the granules during 30 minutes at 40 °C and reduced pressure in a rotating mixer.

Potassium clavulanate granules were prepared as follows:

Potassium clavulanate powder with a water activity of less than 0.2 at 25 °C was mixed with microcrystalline cellulose (Avicel® PH112 with a water activity of less than 0.2 at 25 °C). The mixture was then fed to a roller compactor. The produced compacts were milled with an oscillating Frewitt sieve equipped with a screen with 1000 μm apertures.

The milled material was classified using a vibration sieve equipped with a 420 μm screen on top and a 150 μm screen equipped with an air jet system on the bottom. The material coming from the top of the 420 μm screen and from the top of the 150 μm screen was transferred to a batch mixer, the fine material from the bottom of the sieve was transferred back to the roller compactor. After homogenisation of the granules in the batch mixer, the granules were ready for further processing into tablets.

The tablets were prepared as follows:

Potassium granulate granules (1.52 kg) with a potency of 41.1% clavulanic acid, amoxicillin trihydrate granules (2.925 kg) with a potency of 85.5% amoxicillin, 0.047 kg magnesium stearate, and 0.162 kg microcrystalline cellulose (Avicel® PH112 with a water activity of less than 0.2 at 25 °C). were mixed.

Tablets were pressed using a Korsch EKO excenter tablet press with the following characteristics:
diameter 18 mm, weight 950 mg, thickness 6 mm, hardness between 110 and 150 N, disintegration in water of 20 °C in less than 60 seconds, dissolution of the labelled amount of amoxicillin within 30 minutes by using the method as described in the U.S. Pharmacopoeia XXIII 1994, The United States Pharmacopoeial Convention Inc. Rochville MD, USA.

CLAIMS

1. Granules free of excipients.

2. Pharmaceutical granules according to claim 1.

3. Antibiotic and antihypercholesterolemic granules according to claim 2.

4. Granules according to any one of the claims 1-3 wherein the granules are substantially free of solvents.

5. Granules according to anyone of the claims 1-4 wherein granules have a particle size between 50 and 1500 μm, preferably between 125 and 1000 μm.

6. Granules according to anyone of the claims 1-5 wherein the granules are granules of ß-lactams.

7. Granules according to claim 6 wherein the granules are granules of penicillins, preferably amoxicillin, ampicillin, penicillin V, oxacillin, cloxacillin, flucloxacillin, dicloxacillin and pharmaceutically acceptable salts thereof.

8. Granules according to claim 7 wherein the granules are granules of potassium salt of penicillin V, sodium salt of cloxacillin, sodium salt of flucloxacillin and sodium salt of dicloxacillin.

9. Granules according to claim 6 wherein the granules are granules of cephalosporins, preferably cephalexin, cefaclor, cefadroxil and cephradine.

10. Granules according to anyone of the claims 1-5 wherein the granules are granules of tetracyclines, preferably tetracycline, chlortetracycline, oxytetracycline, doxycycline, minocycline, demeclocycline and acid salts thereof, preferably the HCl salt.

11. Granules according to anyone of the claims 1-5 wherein the granules are granules of macrolides, preferably erythromycin, clarithromycin, roxithromycin, azithromycin and stearates, estolates, propionates and ethylsuccinates thereof.

12. Granules according to anyone of the claims 1-5 wherein the granules are granules of lovastatin, simvastatin and pravastatin.

13. A process for the preparation of granules defined in anyone of the claims 1-12, comprising:
- feeding a powder to be granulated to a roller compactor producing compacts,
- milling the compacts to produce granules,
- sieving the granules with a sieving device optionally coupled to the roller compactor to separate the granulates from fine particles of <150 μm, preferably <125 μm,
- optionally recirculating said fine particles to the roller compactor.

14. A process according to claim 13 wherein the sieving device comprises an air jet system.

15. A process according to claim 14, wherein the sieving device stands separately from the roller compactor.

16. Oral dosage forms as tablets, capsules, syrups, sachets, dry instant or ready to use, multiple or single dose produced from granules as defined in anyone of the claims 1-12.

17. Oral delivery form produced from granules as defined in anyone of the claims 1-12 for using as a Dose Sipping device.

18. Pharmaceutical composition comprising granules as defined in claim 7 mixed with a ß-lactamase inhibitor.

19. Pharmaceutical composition according to claim 18 comprising granules of amoxicillin trihydrate mixed with potassium clavulanate.

20. Pharmaceutical composition according to claim 19 comprising granules of amoxicillin trihydrate mixed with granules of potassium clavulanate.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/43 A61K9/16 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 414 115 A (BASF) 27 February 1991 see claims see examples see page 2, line 41 - line 45 see page 3, line 1 - line 3 ---	1,2,4,5, 13
A	DE 22 51 250 A (HOECHST) 2 May 1974 cited in the application see claims see examples ---	1-20
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
3 December 1998	09/12/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scarponi, U

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INTERNATIONAL SEARCH REPORT

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2

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